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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/215,077	12/18/98	PRICE	P 23070-086711

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EXAMINER	
NGUYEN, B	
ART UNIT	**PAPER NUMBER**
1641	15

DATE MAILED: 07/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/215,077	Applicant(s) PRICE ET AL.	
	Examiner Bao-Thuy L. Nguyen	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Reference A35* .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 4/20/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/215,077 is acceptable and a CPA has been established. An action on the CPA follows.

2. Preliminary amendment filed 4/20/01 has been received. Claims 9-17 have been cancelled. Claims 1-8 are pending.

Priority

3. The subject matter of claims 1-8, i.e. correlation of elevated levels of YKL-40 to alcoholic cirrhosis of the liver, first appeared in PCT/US96/07754, filed 8 July 1998; therefore, claims 1-8 receive the benefit of that filling date, and not that of the parent application, serial number 08/089,989.

Information Disclosure Statement

4. The information disclosure statement filed 1/25/00 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein have not been considered.

Reference A35 appears to be a listing of a sequence, however, no explanation as to how this sequence is relevant to the instant application.

In response to the notice to comply in paper no. 9, applicant alleged that the requirement is improper because reference A35 is in the English language and is accompanied by descriptive information, in English, describing the sequence listed therein. In reviewing the record, again, it is maintained that if, when filed by the Applicant, the reference A35 was accompanied by descriptive information, such descriptive information is now separated from the sequence itself. The descriptive information is not currently, and has not been since the first office action dated 02/03/00, in the application file. Therefore, the current record does not have any descriptive

information for reference A35. It is not the Examiner's position that the reference A35 is not material or effective prior art in the instant application. It is the Examiner's position that the reference A35 cannot be evaluated to determine if it is or is not effective prior art or is material to the instant application because the reference A35 is listed as an amino acid sequence with no other identifiers. For example, how is it possible to determine from an amino acid sequence what it is a sequence of? In an effort to fully explain this requirement, a copy of the reference A35 is attached for Applicant's information. This one piece of paper listing an unknown amino acid sequence and no other identifiers is reference A35.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening the presence of alcoholic cirrhosis of the liver which is associated with degradation of connective tissue containing YKL-40 in a patient suspected of having alcoholic cirrhosis of the liver, does not reasonably provide enablement for a method of screening for a disease state associated with cirrhosis of the liver in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in art, and (8) the breadth of the claims.

The nature of the invention -- the invention is directed toward the identification of a circulating protein associated with extracellular fiber matrix metabolism in mammalian

connective tissues. Specifically, it is directed to assays for the detection and quantitation of YKL-40 and relating it to a specific disease in a patient suspected of having such a disease.

The state of the prior art -- Applicant's post-filing publication, i.e. Johansen et al (Brit. J. Rheum. 31:949, 1993), equates YLK-40 with a protein found in synovial cells by Nyirkos et al (Biochem. J. 268:265, 1990). Nyirkos et al teach that according to the N-terminal sequence of the protein, that "this protein is the human homologue of bovine [mammary] protein isolated from non-lactating cows" (see page 267, column 2, discussion), and Applicant's own discussion states that YKL-40 has been discovered to be elevated in patients with a metastasis of breast cancer cells and persons with join diseases including rheumatoid arthritis and osteoarthritis. The prior art is silent on the correlation between elevated level of YKL-40 in samples such as blood, plasma and serum, and cirrhosis of the liver.

The predictability or lack thereof in the art -- as indicated by the prior art, YKL-40 has not been definitely linked to one specific disease nor has a particular amount been shown to be indicative of one disease over another. While it is possible to screen for the presence of a disease which is associated with degradation of connective tissue, by detecting elevation in the level of YKL-40 in patients suspected of having a disease, as compare to normal level, it has not been possible to identify one particular disease, e.g. alcoholic cirrhosis of the liver, in a mammal as indicated by the elevation of YKL-40.

The amount of direction or guidance present -- appropriate guidance is provided by the specification to screen for the presence of the degradation of connective tissue by detecting elevated levels of YKL-40. However, no guidance is available to teach a skilled artisan how to identify the presence of alcoholic cirrhosis of the liver in a mammal by the elevation of YKL-40. In other words, how would one be able to determine that a blood test showing an elevation of YKL-40 is related to alcoholic cirrhosis of the liver if one does not suspect that the person, i.e. patient, might be suffering from such a disease. The elevation of YKL-40 may be related to several different conditions as shown by the specification.

The presence of absence of working examples -- a working example is provided indicating that YKL-40 level is elevated in patients with alcoholic cirrhosis as compare to patients with normal liver functions. However, other examples are also present showing that elevated YKL-40 levels are also detected in patients with rheumatoid arthritis or other joint

disease and in those with breast cancer. Thus, the instant specification further demonstrate that YKL-40 level cannot be related to one specific disease in any mammal; rather, it may be related to a disease, i.e. alcoholic cirrhosis of the liver, in a patient suspected of having such a disease.

The quantity of experimentation necessary -- it would be undue experimentation for a skilled artisan to make and use the invention as claimed.

The relative skill of those in the art– the level of skill in the art is high.

The breadth of the claims -- the instant claim is directed toward a method of screening for a disease state associated with cirrhosis of the liver in a mammal by comparing the measured level of YKL-40 in a biological sample of the mammal to that of a normal, healthy mammal, wherein a statistically significant difference indicates the presence of cirrhosis.

Elevation of YKL-40 in a patient can be due to a number of different diseases, and no particular amounts have been shown to be indicative of one disease over another; therefore, while it may be possible to screen for a specific disease in a patient suspected of having such disease, it is not possible to identify the presence of a specific disease in any mammal by measuring the YKL-40 as claimed.

In view of the teachings of *In re Wands*, 8 USPQ2d 1400, it has been determined that the level of experimentation required to correlate an elevation in the level of YKL-40 to the presence of cirrhosis of the liver in any mammal is undue. It has been set forth above that 1) the experimentation required to measure and correlate the elevation in the level of YKL-40 to the presence of cirrhosis of the liver in a mammal would be great as 2) there are experiments provided that indicate that the elevation in the level of YKL-40 is indicative of specific disease, e.g. alcoholic cirrhosis of the liver, only in a patient suspected of having such a disease, 3) there are no proper guidance for how to distinguish between one degenerative disease from another ,in any mammal, using the elevation in YKL-40 in the instant specification, 4) the nature of the invention is a correlation between an elevated level of YKL-40 in a biological sample of a patient suspected of having alcoholic cirrhosis of the liver as compare to that of normal, healthy mammal, 5) the relevant skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by Johansen et al and Nyirkos et al, described above, and lastly 7) the claims broadly recite a method of screening for a disease state associated with cirrhosis of the liver in a mammal by comparing the measured level of YKL-40 in the sample

with those of a normal sample, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 5,935,798. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '798 patent is a generic method for screening for the presence of a disease state which is associated with degradation of connective tissue containing YKL-40 in a mammal wherein a statistically significant difference indicates the presence of the disease. And the instant invention claims a specific disease, i.e. cirrhosis of the liver, associated with statistically significant elevation in the level of YKL-40 in a mammal. Because any member of a genus, i.e. a species, anticipates the genus.

Allowable Subject Matter

9. The following claim, drafted by the examiner and considered to distinguish patentably over the art of record in this application, is presented to applicant for consideration:

Claim 1: A method of screening for the presence of [for a disease state associated with] alcoholic cirrhosis of the liver which is associated with degradation of connective tissue containing YKL-40 in a [mammal] patient suspected of having alcoholic cirrhosis of the liver, said method comprising:

measuring the level of YKL-40 in a biological sample of the patient [mammal]; and

comparing the level to that of a normal, healthy mammal,

wherein a statistically significant difference indicates the presence of said [disease state] alcoholic cirrhosis of the liver in said patient.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao-Thuy Nguyen whose telephone number is (703) 308-4243. The examiner can usually be reached Monday, Wednesday and Thursday, from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bao-Thuy Nguyen
Primary Patent Examiner
Group Art Unit 1641
July 12, 2001

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AGAAGAAGCTGGCCAAGGATAT[redacted]GAGCAACCACCATGGACCAGAAGTCTCTCTG[redacted]CAG
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